14. (Amended once) A method of ameliorating psychotic major depression in a patient in need thereof comprising administering to the patient [a] mifepristone in a daily amount of about 8 to 12 mg per kilogram of body weight per day, wherein the administration continues for a period of about 4 days.

Please cancel claim 21.

REMARKS

THE INVENTION:

This invention is the discovery that psychosis can be effectively controlled by antagonizing the glucocorticoid (type II) receptors in the brain of individuals who are suffering from psychotic major depression [PMD]. The following background may facilitate the Examiner's appreciation of the importance of the invention. As explained in the specification, psychosis is not a disease—it is a symptom of a disease, like a runny nose is a symptom of hay fever (pollen) and colds (virus).

Psychosis is defined as a faulty perception of reality. This can be in two forms, e.g. hallucinations and delusions. Hallucinations are visual (seeing things that do not really exist) or auditory (hearing voices) or tactile-sensations (such as spiders crawling on your arms). Delusions are defined as profoundly illogical thinking. They are the logic of our dreams (you are the Messiah; or, my wife will kill my children, therefore I must kill them first).

Prior to this invention, it was known that some antipsychotic drugs (APD) antagonized dopamine receptors. Co-inventor, Dr. Schatzberg, is an originator of a theory that elevated cortisol levels were partly responsible for over production of dopamine or activating or sensitizing dopamine receptors in some patients with psychosis and that cortisol may play an indirect role in psychosis.

Cortisol is a seminal hormone. Like insulin, cortisol is carefully regulated by our bodies, and careful regulation is essential for a normal life. Cortisol is a steroid. The

concentration levels of cortisol in plasma vary in accordance to an internal feedback system that is only partially understood. Cortisol production decreases during the day, increases during sleep, and increases in response to stress. Over production of cortisol is known as Cushing's Syndrome. Under production of cortisol is known as Addison's Disease. Both diseases are serious heath problems leading to fatality if not kept under control.

Cortisol or glucocorticoid is produced by the adrenal gland and binds to at least two intracellular receptors. The primary receptor is the mineralocorticoid receptor. The secondary receptor is the glucocorticoid receptor which is the target receptor identified in the pending claims. Cortisol binds with 10X greater affinity to the mineralocorticoid receptor than to the glucocorticoid receptor. Some believe that the glucocorticoid receptor is primarily a negative feedback loop. If this theory proves correct, when all the mineralocorticoid receptors are filled, the glucocorticoid receptors are progressively filled and the body sends a signal to lower cortisol production. The feedback loop is not fully understood.

It is within this scientific framework that the present invention was discovered. The prior art is replete with work suggesting that inhibition of cortisol synthesis may control neurological diseases, including diseases that have psychosis as a symptom; but, cortisol is like insulin, and you cannot block its synthesis for too long or the patient will die. Both the mineralocorticoid and the glucocorticoid receptors are found in the brain; and, until this invention, it was not known if antagonism of both or either would help treat psychosis.

To avoid confusion by the nomenclature of the prior art, it should be noted that the mineralocorticoid receptor and the glucocorticoid receptors have alternative names. The mineralocorticoid receptor is sometimes referred to as the glucocorticoid type I receptor, and the original glucocorticoid receptor is sometimes referred to as the glucocorticoid type II receptor. Applicants refer to the first nomenclature. This is unambiguously understood by those of skill because mifepristone is known to only bind to the glucocorticoid type II receptor. It has no binding affinity to the type I receptor.

The extension of the prior art involving Cushing's patients to depressed patients who are psychotic with normal cortisol levels is an incredibly important discovery! In every major city in the world there are newspaper stories of unexplainable horror. The single mother whose boyfriend moves out and she drives her car with her two young boys into a lake. The

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middle-aged neighbor with a history of depression, who one evening walks upstairs and guns down the two school teachers living in the upstairs apartment. The day trader in Atlanta who shoots his own family, his colleagues, and then himself. These shocking stories are continually presented to us by the media, but their context is never explained. In many cases, the story ends with the killer committing suicide.

If a psychiatrist were to perform a psychological autopsy on these horrible stories, you would commonly find that the killers have had a history of mental depression; but, they were not considered violent by family or friends. Usually, these individuals are only partially able to work and are supported by their families. Their personal relationships may dissolve, not because of psychosis, but due to the other symptoms of depression. In these patients, psychosis, which is the underlying problem leading to violence, is temporary and is likely triggered by an additional stress like being fired, losing money, or an impending divorce. Remorse leads to greater depression and perhaps to relapse and suicide.

This invention is a paradigm shift in treating depression and other diseases with psychosis as a symptom. Classic antidepressants are not intended to control psychosis. They are directed to MAO production or to blocking reuptake of serotonin. They do control depressed moods; but, they have no effect on cortisol levels, which can lead to psychosis even if the depression is not extremely severe.

Prior workers claimed that blockers of cortisol synthesis such as ketoconazole were useful for treating depression. THEY WERE WRONG. Modernly, these blockers are not deemed helpful for treating depression. Even if they were effective, they are far too dangerous to use for long periods of time as required to treat depression.

STATUS OF THE CLAIMS.

Claims 1-21 are pending. Claims 1-14 and 21 are rejected under §112, second paragraph. Claims 1-21 are further rejected under §103(a).

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AMENDMENTS.

Claims 1 and 14 are amended as suggested by the examiner to include reference to a patient. Claim 1 has been amended to recite psychosis associated with major depression, which finds support throughout the specification; and, more specifically, is recited in claim 2.

REJECTIONS.

35 U.S.C. §112, 2nd paragraph.

Claims 1-14 and 21 were rejected for failing to identify a patient in the preamble. The Examiner kindly suggested language that would overcome the rejection. The claim amendments track the Examiner's suggestion and are believed to fully address the rejection under §112, 2nd paragraph.

35 U.S.C. §103 (a).

Claims 1-21 have been rejected as obvious over Ravaris, Van der Lely, Piazza *et al* and Behl *et al*. Ravaris is described as disclosing that inhibiting the synthesis of cortisol in a patient exhibiting hypercortisolemia is effective at treating depression, including major depression with psychotic features. Van der Lely is cited as teaching that mifepristone reversed psychosis in patients by blocking glucocorticoid receptors. Piazza *et al.* is cited as suggesting that inhibition of endogenous glucocorticoids would be effective at reducing psychotic symptoms in humans. Finally, Behl is cited as suggesting that glucocorticoid receptor antagonists, such as mifepristone, would be effective at reducing neuronal degeneration in Alzheimer's Disease. The Examiner concludes that one of skill reading the references would have a reasonable expectation that glucocorticoid receptor antagonists would be effective at controlling psychosis in humans in the absence of Cushing's Disease.

Ravaris teaches that drugs that inhibit adrenal cortisol synthesis can effectively treat non-psychotic major depression and psychotic depression where that depression is associated with hypercortisolemia. The one patient studied by Ravaris had had Cushing's disease and remained hypercortisolemic. The patient was described at column 5, lines 1-4, as having a cortisol level of 906 μg/24 hours, where normals had corisol levels of between 75-206 μg/24 hours. Therefore, the Ravaris invention clearly addresses patients with

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hypercortisolemia, i.e., those who have not fully recovered from Cushing's Disease. This is a rare population.

The Examiner urges that one of skill would recognize that a cortisol synthesis inhibitor has the same effect as a glucocorticoid receptor antagonist, and one of skill would have a reasonable expectation that a glucocorticoid receptor antagonist would have the same effect as a cortisol synthesis inhibitor such as ketoconazole. Applicants respectfully disagree with this logic. The human body and the cortisol biology in particular are very complex. Accurate predictions in pharmacology are not reasonably expected nor possible. Enclosed with this response as Exhibit 1 is a copy of a review article by Sonino detailing the array of adrenal enzymes that are inhibited by ketoconazole. Figure 2 on page 813 details the eight steps that ketoconazole blocks in the production of adrenal steroids of which cortisol is only a member. Ketoconazole also blocks production of testosterone, estrogen, DHEA and aldosterone. Exhibit 2 provides two articles reporting serious safety issues with long-term use of ketoconazole. For these reasons, use of ketoconazole is too dangerous to be recommended for long-term use which is required for treating depression.

The next two prior art references (Van der Lely and Piazza) involved mifepristone. Mifepristone is an antagonist of the glucocorticoid (type II) receptor. As described earlier, there are two known cortisol receptors. They were first named the mineralocorticoid receptor and the glucocorticoid receptor; but, they are also referred to as glucocorticoid receptors type I and type II, respectively. The primary receptor is the mineralocorticoid receptor (type I). The glucocorticoid receptor (type II) has a significantly lower binding affinity for cortisol than the mineralocorticoid receptor. Mifepristone does not bind to the type I receptor, and the applicants' claims are unambiguously directed to the type II receptor.

This invention is based on the discovery that some forms of psychosis are the result of glucocorticoid receptor activation which leads to excessive dopamine production. There was simply no way of predicting that psychosis in patients with normal cortisol levels could be controlled by the selective inhibition of the minor cortisol receptor. The fact that the activation of a minor receptor is responsible for psychosis makes possible treatment modalities that are far less likely to have side effects than treatments that totally block steroid production

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of an essential hormone like cortisol or an antagonist of the primary receptor with all its many downstream effects.

Van der Lely is cited as teaching that mifepristone reversed psychosis in patients by blocking glucocorticoid receptors; but this is an overly broad interpretation of this work. Van der Lely's work describes the treatment of psychosis in patients with Cushing's Disease with mifepristone. In Cushing's disease, the patient is producing cortisol at 10X the normal rate. The effect of such high levels of cortisol is analogous to redlining an automobile engine hour after hour. These patients have a host of serious medical symptoms beyond depression and psychosis. Other symptoms include obesity, high blood pressure, high blood sugar, acne, muscle weakness, bone weakness and excessive hair growth. Cushing's patients are very sick people usually having cancer of the adrenal or pituitary glands.

One of skill would not have extended the Van der Lely teaching as it related to Cushing's patients to psychosis in depressed patients having normal cortisol levels because exposure to excessive cortisol affects so many aspects of the body. Glucocorticoid receptors targeted by mifepristone are found throughout the body. Therefore, mifepristone would have been viewed as having a global benefit on the Cushing's patients in the Van der Lely trials. The global benefit would have reduced the cortisol stress on the body and alleviated the depression, the psychosis, and a host of other serious symptoms associated with Cushing's disease.

The fallacy of the Examiner's logic is perhaps made more clear by an analogy to using insulin for treating diabetes. High blood pressure is a symptom of diabetes and is one of the many diabetic symptoms ameliorated by insulin treatment, but no one would think of using insulin to treat high blood pressure in non-diabetic patients. Analogously, psychosis is thought to have a variety of different etiologies. Excessive amounts of cortisol in Cushing's patients were not a consideration in psychotic major depressed patients because they have cortisol readings within normal levels.

Piazza (1996) is a non-clinical study, which, owing to the unpredictability of the field, teaches away from the invention. Piazza uses rats to demonstrate that removal of a rat's adrenal glands lowers dopamine production and that exogenous corticosterone can induce dopamine release. Piazza suggests that glucocorticoids might sensitize the brain to become

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psychotic through stimulation of dopamine. Piazza is primarily concerned with psychosis of schizophrenia.

In the same paragraph where Piazza suggests that antiglucocorticoid drugs might "open new therapies for behavioral pathologies" they teach away from the use of the very drugs that form the basis of the subject invention. On page 15449, they give several reasons why glucocorticoid receptor antagonists are not likely to work to treat psychosis. The authors specifically state that these drugs do not readily cross the blood brain barrier and are not specific enough. He also suggests that inhibitors of glucocorticoid synthesis (ketoconazole) would not be useful as anti-psychotics because they are poorly specific, "direct non-specific effects on brain function" and increase glucocorticoid precursors, that even if with lower affinity, can still bind to corticosterioid receptors. They go on to state, "these observations could explain why the potential APD (antipsychotic drug features of antiglucocorticoid drugs have not yet been revealed...."

Behl is a non-clinical paper which reports on the fact that cortisol sensitizes brain cells to the toxicity of glutamate and amyloid β-protein. Mifepristone reverses the sensitization of the cells, and Behl speculates that hypercortisolism (Cushing's Disease) could predispose the brain to damage. There is no mention of psychosis in Behl.

Having commented on the references as individual pieces of prior art, applicants will now address the combined teachings of the references. As the examiner knows, a *prima facie* case of obviousness requires the PTO to identify the salient elements of the claim, provide objective reasons for combining the elements and a reasonable expectation that once combined, the elements will perform as intended. Clearly, the Examiner has identified the elements of the invention, i.e., psychotic, depressed patients and glucocorticoid receptor antagonists such as mifepristone. The remainder of this response will establish that the other two elements of the *prima facie* case of obviousness have not been legally set forth.

Lack of motivation.

Motivation can be defined as the mental force that pushes those of skill to combine various elements of the prior art together. The Examiner cannot simply pick and choose among random statements of the prior art to set forth motivation adequate to present a

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legally proper *prima facie* case of obviousness. He must fairly weigh all the prior art, both motivating for the combination and against the combination, to reach an objective conclusion. *Akzo N.V. v USITC,* 808 F.2d 1471, 1481 (Fed. Cir. 1986).

In the instant situation, the Examiner first states facts about each reference and then, without adequate objective reasoning, concludes: "clearly the references in combination suggest that glucocorticoid receptor antagonists such as mifepristone would be effective at ameliorating psychosis in humans." But Piazza's last words on page 15449 are evidence that those of skill would not conclude as the Examiner has concluded. In deed, Piazza *et al.* are not sure whether the mineralocorticoid or the glucocorticoid receptor should be blocked, or whether the entire biosynthetic pathway should be blocked. Moreover, they teach against the use of mifepristone by specifically motivating against its use for treating psychosis based on their erroneous belief that it cannot cross the blood brain barrier and is not receptor specific. Finally, Piazza expressly states that the idea of treating psychosis through the "blockade of certain central effects of these hormones" is a medical theory not yet proven true because the existing drugs, both synthesis inhibitors and receptor antagonists, are simply inadequate to properly test the theory.

Applicants of the subject invention went contrary to this teaching and demonstrated that mifepristone does have utility for treating psychotic patients with normal cortisol levels.

In summary, even with evidence of Van der Lely and Ravaris, those of skill such as Piazza, were still not motivated to try glucocorticoid receptor antagonists on non-Cushing's psychotic patients. In urging that there is adequate motivation, the Examiner is ignoring the teachings of Piazza and using the applicants' own clinical success to complete the motivation part of the *prima facie* case of obviousness. The law requires that motivation come from a fair reading of all the references. Motivation is not properly set forth when it is supported by taking select language out of context from the prior art and combining that language with the applicants' facts presented in the subject application.

Unpredictability.

In addition to a lack of sufficient motivation to combine elements, the field of drug discovery for mental diseases is a highly unpredictable art. Below, applicants provide

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objective reasons why there is insufficient predictability in this art for those of skill to have a reasonable expectation that antagonizing the glucocorticoid receptor would result in an effective anti-psychotic treatment.

This invention arises out of the inventors' belief that psychosis is caused by excessive production of dopamine or sensitization of the dopamine receptor, but this is not a universally accepted theory of psychosis. The Reynolds article in *TiPS* (Exhibit 3) at pages 116 to 117 explains that the dopamine theory has a school that views psychosis as caused by increased dopamine activity but that another school holds that psychosis is caused by inhibition of dopamine activity. Reynolds cites to a first study of schizophrenic brain tissue that had elevated D_2 receptors, but then a study of young schizophrenics using a positron emission tomography determined that no upregulation was noted in these psychotic patients and that the former work was likely due to the antipsychotic medication the patients were taking.

Even if one assumes that increased dopamine activity is responsible for psychosis, the excess or upmodulation is not believed to arise from a single cause. Accordingly, this invention is not expected to have utility against all forms of psychosis. For example, schizophrenics appear to have a hard wiring problem and the inventors do not believe that schizophrenics are treatable by antagonizing the glucocorticoid receptor.

As further evidence of the unpredictability of the relevant art, applicants refer to Dr. Belanoff's Rule 132 Declaration where he describes clinical trials with patients having schizoaffective disorder. These are schizophrenic patients who also display depression. In these trials, Dr. Belanoff treated two patients with mifepristone at doses recognized to provide relief from psychosis in depressed patients. There was no significant improvement with either patient, and the trials have been terminated.

Blocking cortisol production along with a host of other adrenal hormones is reported to alleviate psychosis in depression associated with hypercortisolemia (as in a former Cushing's Disease patient) (Ravaris) and blocking the glucocorticoid receptor using mifepristone reversed psychosis in active Cushing's patients (Van der Lely). It is tempting to use these two references to predict success for treating psychosis arising from other diseases, but these facts do not lead to a reasonable expectation that a similar therapy would work for psychotic patients with normal levels of cortisol (non-Cushing's patients).

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The extension of the prior art to non-Cushing's patients was not predictable. The human body is an enormously complex and unpredictable milieu. Cushing's patients have been exposed for long periods of time to 10X the normal levels of cortisol. Permanent damage has been done to their circulatory, muscular and nervous systems. The number and location of mineralocorticoid and glucocorticoid receptors may have been altered. In Cushing's patients, cortisol is not the only adrenal steroid that is over produced. Testosterone and estrogen are also elevated. Cushing's patients are often cancer patients and have been exposed to the mental stress of a serious disease. They have compromised immune systems and have generally been exposed to a large variety of potent drugs.

The Examiner should note that the relationship between cortisol and dopamine activation is not understood. The two major cortisol receptors have only recently been identified and may not be the only ones produced by the body. They are intracellular receptors that bind to the adrenal steroids that, in combination, then bind to specific regions of DNA and activate transcription of proteins. The cascade leading to dopamine production could be a single step or multiple steps. Cortisol-induced over production of dopamine might not be the dominant control mechanism of dopamine production in normal, non-Cushing's patients. The observed relationship might only be a minor accident of evolution and be limited to patients with Cushing's syndrome.

Having provided objective reasons for the unpredictability of the relevant art. Let us look at some of the theoretical alternatives that applicants faced as they began their work. The prior art, when fairly read, could support a theory that the cause of dopamine overproduction (psychosis) is due to activation of the glucocorticoid receptor in Cushing's Disease patients by cortisol. The Examiner could extrapolate from these patients to non-Cushing's Disease patients with psychosis, but this selective logic requires that the Examiner ignore other equally plausible theories—that if true would predict that mifepristone would not work on patients with psychotic major depression.

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a. Lower concentration of glucocorticoid receptors.

Here we presume that exposure to high levels of cortisol leads to a general lowering of the concentration of glucocorticoid receptors in the brain and that prolonged occupation of these receptors by cortisol induces psychosis. In this first scenario, Cushing's patients have less target for mifepristone to bind to as compared to non-Cushing patients. In the competition for receptor occupation between mifepristone and cortisol, mifepristone would not be as effective in depressed, psychotic patients because they have more endogenous receptors than Cushing's patients.

b. Excess concentration of glucocorticoid receptors.

Let us now presume that excess cortisol in Cushing's disease leads to an increase in the absolute numbers of glucocorticoid receptors compared to the numbers found in the normal population, and again, that cortisol activation of these additional receptors leads to high dopamine activation and psychosis. Mifepristone would therefore work selectively in psychotic Cushing's patients because the psychosis is induced by the presence of additional receptors. However, psychosis in patients with normal cortisol levels and normal concentrations of glucocorticoid receptors would not respond to mifepristone because their psychosis would not be due to occupation of additional glucocorticoid receptors.

c. Lower concentration of mineralocorticoid receptors.

For this third scenario, let us presume that psychosis in Cushing's patients is due to a lowering of the absolute number of mineralocorticoid receptors in the patient's brains. This reduction in receptor numbers permits activation of dopamine pathways, which induces psychosis. This activation is then offset by mifepristone when it antagonizes the glucocorticoid receptor and generates a signal to the mineralocorticoid receptors to lower dopamine activity. Now let us assume that in non-Cushing's associated psychosis, mineralocorticoid receptors are present in normal numbers, but they are not functioning properly. In the non-Cushing's patients, two possibilities for mifepristone failing to treat psychosis are apparent. First, the mineralocorticoid receptors are not functioning normally, which leads to the psychotic state, and due to their abnormal function they cannot respond to a signal from an antagonized glucocorticoid receptor. Alternatively, the mineralocorticoid receptors could be functioning abnormally and remain responsive to signals from antagonized

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glucocorticoid receptors, but due to their high numbers of receptors in normals, the psychotic state is maintained despite the presence of mifepristone.

d. Miscellaneous possibilities.

One could also presume that dopamine levels are controlled in normal brains by a delicate balance of receptor occupation by adrenal steroid hormones and that cortisol does not affect the absolute numbers of receptors. In this case, the Cushing's patients with psychosis are simply a unique population that is helped by mifepristone. Alternatively, psychosis in non-Cushing's patients could have been the result of a problem downstream of the transcription activation of the two receptors and unrelated to cortisol levels. In this case there would be no benefit to non-Cushing's patients by using mifepristone.

These are only a handful of the plausible scenarios that preexisted when the applicants began their clinical studies that led to this important discovery. As one reflects upon the complexity of the human nervous system and how very little of that system that we understand, it is clear that the prior art fails to provide the needed level of expectation of success that is required to set forth a proper *prima facie* case of obviousness.

Applicants have responded to the outstanding rejection under §103 by urging that the prior art predicted failure and that the level of predictability is so high in the relevant art that extrapolations from non-clinical work in animals and from clinical results using different and non-analogous patient populations cannot provide the requisite expectation of success to set forth a proper *prima facie* case of obviousness. Applicants believe that the rejection is fully rebutted. Reconsideration and withdrawal of the rejection is requested.

Additional art.

Applicants have supplied an IDS with this response. Some of the references are discussed below.

The Murphy reference describes four patients being treated with mifepristone for depression. Although some of the patients had experienced psychosis prior to treatment, none of the patients were reported as having psychosis at the time of treatment. It is a standard protocol in depression trials to eliminate persons with active psychosis in such trials because it is considered a separate disease. The medical treatments for depression and psychosis do not

overlap, and test results would be artificially skewed if psychotics were included in the trials evaluating the effects of a drug for treating depression. Evidence of the recognized differences between major depression and psychotic major depression is provided in Exhibit 4. Exhibit 4 is a copy of pages 479-493 of The Textbook of Psychiatry. The copied pages are from Chapter 13 entitled, "Mood Disorders." On page 493, second column, the authors note that when the depressed patient becomes psychotic, "a unique disorder has evolved."

Murphy's work is also evidence of the unpredictability of the art of drug discovery for mental diseases. Murphy represents a failed clinical trial. Using mifepristone to treat depression was apparently not practical. Treating depression involves long term use of mifepristone and only one of the four persons in the trial was able to complete the 8 week trial due to side effects. According to the authors, their results were "not adequate to judge the efficacy of RU 486...." The authors suggest that further studies were warranted, but the drug manufacturer apparently disagreed and refused to continue support for the trials.

Long-term use of mifepristone is not indicated for treating psychosis. As described in the attached Rule 132 Declaration of Dr. Belanoff, psychosis associated with major depression is a temporary event, and, once reversed by "short term" use of mifepristone (less than a week), the depression component of the mental disorder is treated with non-glucocorticoid antagonist treatment modalities.

The French PCT application of Oberlander *et al.* is not prior art, but is brought to the Examiner's attention because a U.S. application may be pending. Like Murphy, this reference appears superficially to be pertinent because the word "psychosis" is used. However, the reference is actually describing psychosis of diseases unrelated to applicants' work. The relevant paragraph from page 3, line 4-14 of the specification, has been translated.

> The term psychosis encompasses, in particular, schizophrenia and manic states as defined in the DSM-IV. Addiction refers to any consumption compulsive behavior where there is a physical or biological dependence on the consumed object. Addictions include, in particular, addiction to drugs, such as opium or derivatives, psychostimulating drugs, barbiturate derivatives, cannabis or derivatives thereof, addiction to tobacco or alcohol, eating disorders such as bulimia, and compulsive behaviors such as the "pathological game."

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According to the plain meaning of the translation, the French inventors believe that the psychoses treatable with mifepristone are **schizophrenia** and **mania**. All schizophrenics are psychotic and the psychosis is often used as a synonym for schizophrenia. Mania is the opposite of the psychosis associated with depression and there is no reason to believe that it is associated with dopamine. Mania is often associated with the delusion that you are larger than life such as the belief you are a god, Christ, or the president. The pending claims do not read on these diseases and it would be surprising if mifepristone were shown to work for the diseases set forth by Oberlander. We refer the Examiner to Dr. Belanoff's lack of success with schizoaffective patients.

It should be noted that the Piazza paper is by this same research team, and the Piazza paper is clearly investigating mifepristone for its potential to treat psychosis in schizophrenics and not those persons with major depression. At page 15445, column 1, the authors note the effects of dopaminergic transmission in psychosis and addiction. Later in column 2 of that page, the authors confirm the nature of their interest when they refer to reports of hypersensitivity to the dopaminergic effects of glucocorticoids in schizophrenic patients.

If there is a corresponding US patent application to PCT FR 97/02321, its potential use as a provisional §102(e)/103 reference is acknowledged. As mentioned above, the predictability of the use of mifepristone to treat psychosis arising from different diseases is low. Again, applicants refer the Examiner to the evidence presented by Dr. Belanoff in his declaration where he describes his failure to successfully treat patients suffering from schizoaffective disorder with mifepristone.

The Schatzberg papers (1984 & 1985) are theoretical papers. The authors discuss the possible connection between the psychosis in patients and hypercortisolemia (see pages 59 and 61 of *J. Psychiat. Res.*). There is no mention of mifepristone or of antagonizing the glucocorticoid receptor.

Applicants believe that all the outstanding concerns raised by the Examiner have been fully addressed and overcome. The claims appear to be in condition for allowance. Should the Examiner believe that a telephone communication would expedite the prosecution

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of this application in any manner, he is invited to call the undersigned attorney at the number provided below.

Respectfully submitted,

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Enclosures: Petition to Extend Time
Exhibits 1-4
Information Disclosure Statement w/ PTO-1449
Rule 132 Declaration

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